FDA Arthritis Advisory Committee Meeting May 8, 2012 – Introductory Remarks

sBLA 125249: Arcalyst (rilonacept) for Prevention of Gout Flares During Initiation of Uric Acid-Lowering Therapy

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Arcalyst (rilonacept)

- Interleukin-1 (IL-1) inhibitor that acts as a soluble decoy receptor that binds IL-1 and prevents its interaction with cell surface receptors
- Approved in 2008 for the rare genetic disorder Cryopyrin-Associated Periodic Syndrome (CAPS) at a dose of 160 mg subcutaneously (SC) once weekly, after an initial loading dose of 320 mg for adults
  - Dose is 2.2 mg/kg once weekly after a loading dose of 4.4 mg/kg in children ages 12 to 17 years

Proposed Use

- Indications and Usage
  - "…for the prevention of gout flares during initiation of uric acid-lowering therapy in adult patients with gout.
  - Arcalyst has not been studied for longer than 16 weeks in this clinical setting."
- Dosage and Administration
  - "Adult patients 18 years and older: Initial loading dose is 160 mg (two 80 mg injections) and continue with 80 mg once weekly. The recommended duration of use is 16 weeks in patients initiating uric acid-lowering therapy."

Phase 3 Program in Gout

Study	Design/ Duration	Treatment Groups	N	Countries/ Regions
810	R, DB, PC 16 Weeks	Rilonacept 80 mg SC QW Rilonacept 160 mg SC QW Placebo	80 71 79	US/Canada
816	R, DB, PC 16 Weeks	Rilonacept 80 mg SC QW Rilonacept 160 mg SC QW Placebo	82 84 82	Germany, S. Africa, Taiwan, India, Indonesia
815 Safety Study	R, DB, PC 16 Weeks	Rilonacept 160 mg SC QW Placebo	985 330	US, Germany, S. Africa, Taiwan, India, Indonesia

Key: R=randomized; DB=double-blind; PC=placebo-controlled; SC=subcutaneous QW=once weekly

Efficacy Considerations

- Mean number of gout flares per patient
  - Flare defined as
    - Typical acute articular pain requiring treatment
    - Presence of 3 of 4: joint swelling, redness, tenderness, pain
    - AND rapid onset, or ↓ range of motion, or warmth, or symptoms typical to previous
  - Placebo group ~1, rilonacept ~0.3 flares
  - ~50% of patients in the placebo group did not experience a flare
- Mean number of gout flare days per patient
  - Rilonacept treatment resulted in ~ 4 less flare days/patient
- Rescue medication use
  - Rilonacept treatment groups used 4 to 5 fewer days of rescue meds (non-steroidal anti-inflammatory drugs & glucocorticoids)
- 16 week duration limitation
  - Increase in patients experiencing flare after rilonacept treatment was discontinued at week 16

Safety Considerations

- Lack of safety data for use beyond 16 weeks, which is not typical of programs for immunosuppressants
- Increased incidence of malignancy with rilonacept

Purpose of Proceedings Before an Advisory Committee (21 CFR 14.5)

a) An advisory committee is utilized to conduct public hearing on matters of importance that come before FDA, to review the issues involved, and to provide advice and recommendations to the Commissioner

b) The Commissioner has sole discretion concerning action to be taken and policy to be expressed on any matter considered by an advisory committee

Risk-Benefit Considerations

- Patient population
  - Not a refractory or particularly difficult-to-treat population
  - Half of patients receiving no treatment did not even experience a flare
- Efficacy limitations
  - Apparent treatment effect sizes with rilonacept are in the context of no treatment in the control group
  - Treatment period of 16 weeks may not be long enough; patients flared after treatment
- Safety limitations
  - Duration of 16 weeks may not be adequate to demonstrate many toxicities

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Overview of the Clinical Program

Supplemental Biologic License Application (sBLA) for Rilonacept for Gout Flare Prophylaxis

Deborah Seibel, M.D.
Medical Officer, Division of Pulmonary, Allergy, and Rheumatology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Outline

- Overview of the Clinical Program
  Deborah Seibel, MD
  Clinical Reviewer, DPARP, CDER, FDA
- Statistical Summary of Efficacy and Safety
  Ruthanna Davi, PhD
  Statistical Reviewer, DB II, CDER, FDA
- Efficacy, Safety, and Risk-Benefit Considerations
  Banu A. Karimi-Shah, MD
  Clinical Team Leader, DPARP, CDER, FDA

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  Clinical Team Leader, DPARP, CDER, FDA

Objectives

- To discuss the efficacy claim for rilonacept in the prevention of gout flares during initiation of uric acid lowering therapy for 16 weeks in adult patients with gout
- To discuss the adequacy of the safety database to allow for the evaluation of potential safety issues

Rilonacept for Gout

- Proposed Indication: prevention of gout flares during initiation of uric acid-lowering therapy in adult patients with gout
  - *novel indication*

- Proposed Dosing Regimen: 160 mg SC loading dose, 80 mg SC once weekly
  - *treatment duration limited to 16 weeks*

Overview of Regulatory History

- 2008 End-of-Phase 2 meeting
  - Discussions initiated regarding adequacy of proposed safety database
  - FDA stated that patients should be treated in a manner and for a duration consistent with the product's proposed use in clinical practice
- 2010 Pre-sBLA meeting
  - Adequacy of the safety database revisited
    - Applicant proposed 1000 to 1500 patients treated for 16 weeks
    - Applicant contended that the proposed limited duration of use is different than a chronically administered immunosuppressant
  - FDA suggested targeting a population that would allow for a more favorable risk-benefit profile

Overview of Early Development

Acute Flare Treatment – Study 814

- Rilonacept 320 mg SC alone or in combination with indomethacin did not produce a greater reduction in pain, as compared with indomethacin alone

Flare Prophylaxis (Proof of Concept) – Study 608

- Chronic active gout
- Slow recruitment: no further study in this subset of patients

Flare Prophylaxis (Phase 2) – Study 619

- Patient population similar to Phase 3 studies
- Different definition of gout flare
- Used by Applicant to support 16 week treatment duration

Phase 3 Studies

Study	Design/ Duration	Treatment Groups*	N	Countries/ Regions
810	R, DB, PC 16 Weeks	Rilonacept 80 mg SC QW Rilonacept 160 mg SC QW Placebo	80 81 79	US/Canada
816	R, DB, PC 16 Weeks	Rilonacept 80 mg SC QW Rilonacept 160 mg SC QW Placebo	82 84 82	Germany, S. Africa, Taiwan, India, Indonesia

* All patients were initiated on urate-lowering therapy with allopurinol 300 mg titrated upward by 100 mg every 2 weeks until serum uric acid < 6 mg/dL was achieved.

Key: R=randomized; DB=double-blind; PC=placebo-controlled; SC=subcutaneous QW=once weekly

Dose Selection

- No formal dose ranging studies were conducted in support of the proposed gout indication
  - Dose selection based on pharmacokinetics data to estimate the relative rate of IL-1 production in different disease states and its neutralization by rilonacept
  - Loading dose carried over from CAPS indication
- Two doses, 80 mg SC and 160 mg SC, included in phase 3 efficacy studies
- Dose proposed for marketing: 80 mg SC QW

Evaluation of Efficacy

- Population
  - History of gouty arthritis
    (American Rheumatism Association criteria)
  - Serum Uric Acid ≥ 7.5 mg/dL at screening and no contraindication to allopurinol
  - History of ≥ 2 gout flares in the previous year
- Prohibited Medications
  - Nonsteroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, colchicine as prophylaxis
- Permitted Medications
  - NSAIDs and glucocorticoids as rescue

History of Medications Used to Treat Flares

	Study 810			Study 816		
	Placebo	RIL 80 mg	RIL 160 mg	Placebo	RIL 80 mg	RIL 160 mg
	N = 79	N = 80	N = 81	N = 82	N = 82	N = 84
	Percent of patients					
NSAIDs alone	61	58	58	59	61	63
Steroids alone	4	6	4	2	7	11
Colchicine alone	23	21	21	16	21	33
Steroids & NSAIDs	6	5	5	24	23	26
Other	24	19	30	20	15	17

Baseline Disease Characteristics

	Study 810			Study 816		
	Placebo	RIL 80 mg	RIL 160 mg	Placebo	RIL 80 mg	RIL 160 mg
	N = 79	N = 80	N = 81	N = 82	N = 82	N = 84
# Gout flares in prior year, Mean (SD)	5 (4)	5 (3)	5 (4)	7 (7)	7 (5)	7 (6)
Duration of Typical Flare, Mean Days (SD)	5 (4)	5 (3)	5 (4)	4 (2)	4 (2)	4 (3)
Polyarticular Gout (%)	80	69	65	83	77	80
Tophi Present (%)	10	13	10	22	26	25

Evaluation of Efficacy: Endpoints

- Primary Endpoint
  - Number of gout flares per patient, Day 1 to Week 16
- Secondary Endpoints
  - Proportion of patients with at least one gout flare, Day 1 to Week 16
  - Number of gout flare days per patient
- Exploratory Endpoints
  - Number of days rescue medications required

Evaluation of Efficacy

- Definition of Gout Flare (810 and 816)
  - Patient-reported acute articular pain typical of a gout attack that was deemed (by patient and/or investigator) to require treatment (and was treated) with NSAIDs or steroids, ***AND***

≥ 3 of the following:	AND	≥ 1 of the following:
Joint swelling Redness Tenderness Pain		Rapid onset pain ↓ Range of motion Joint warmth Symptoms similar to prior gout flare

Safety Database

Study	Design/ Duration	Treatment Groups	N	Countries/ Regions
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Statistical Summary of Efficacy and Safety

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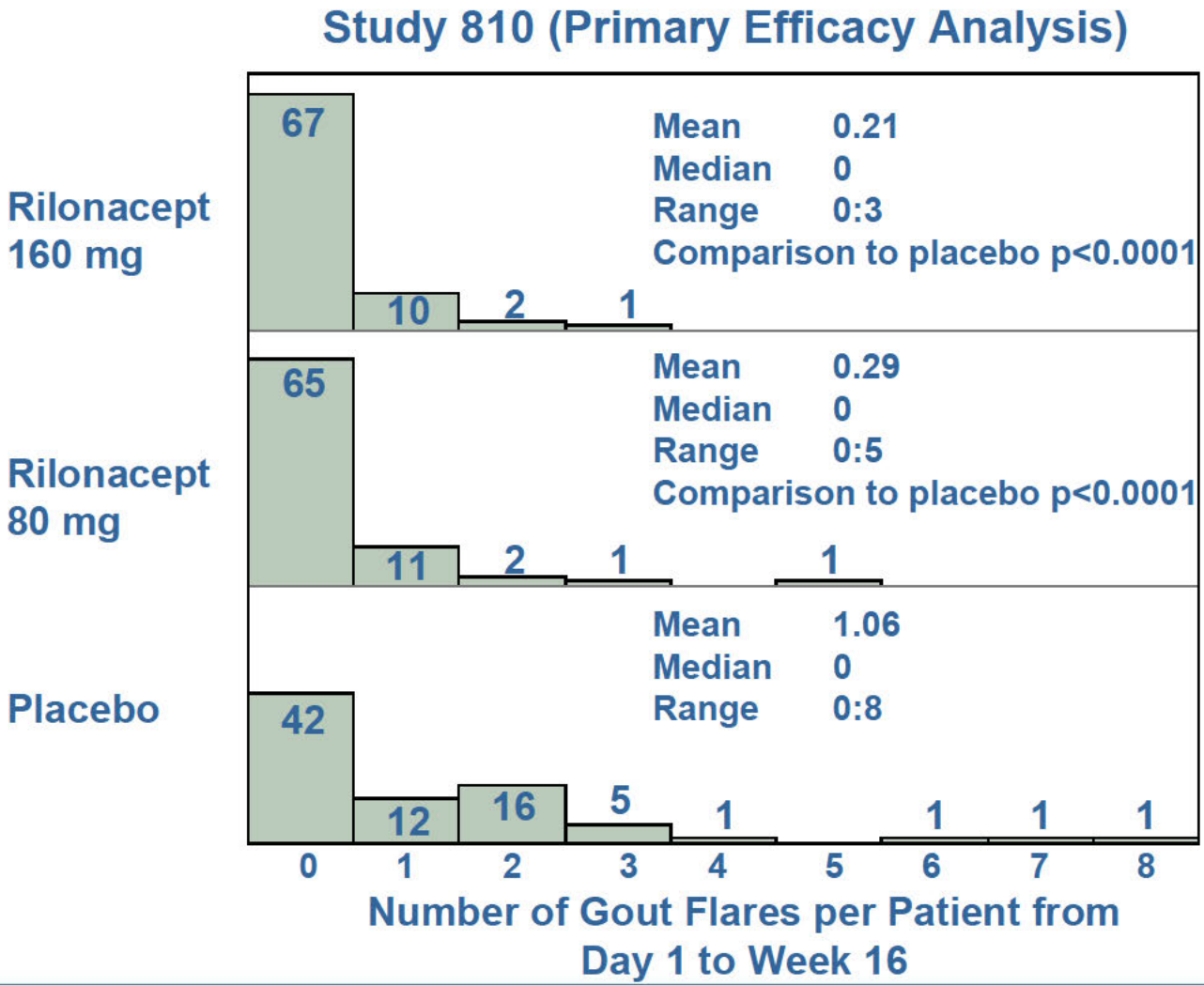
Focus

- Efficacy (Studies 810 and 816)
  - Number of gout flares per patient from day 1 to week 16 (primary endpoint)
  - Proportion of subjects with at least one flare from day 1 to week 16 (multiplicity-corrected secondary endpoint)
- Safety (Studies 810, 816, 815 and 619)
  - Rate of malignant neoplasms
- Benefit-Risk
  - Number needed to treat to benefit
  - Number needed to treat to harm

Number of Gout Flares per Patient from Day 1 to Week 16

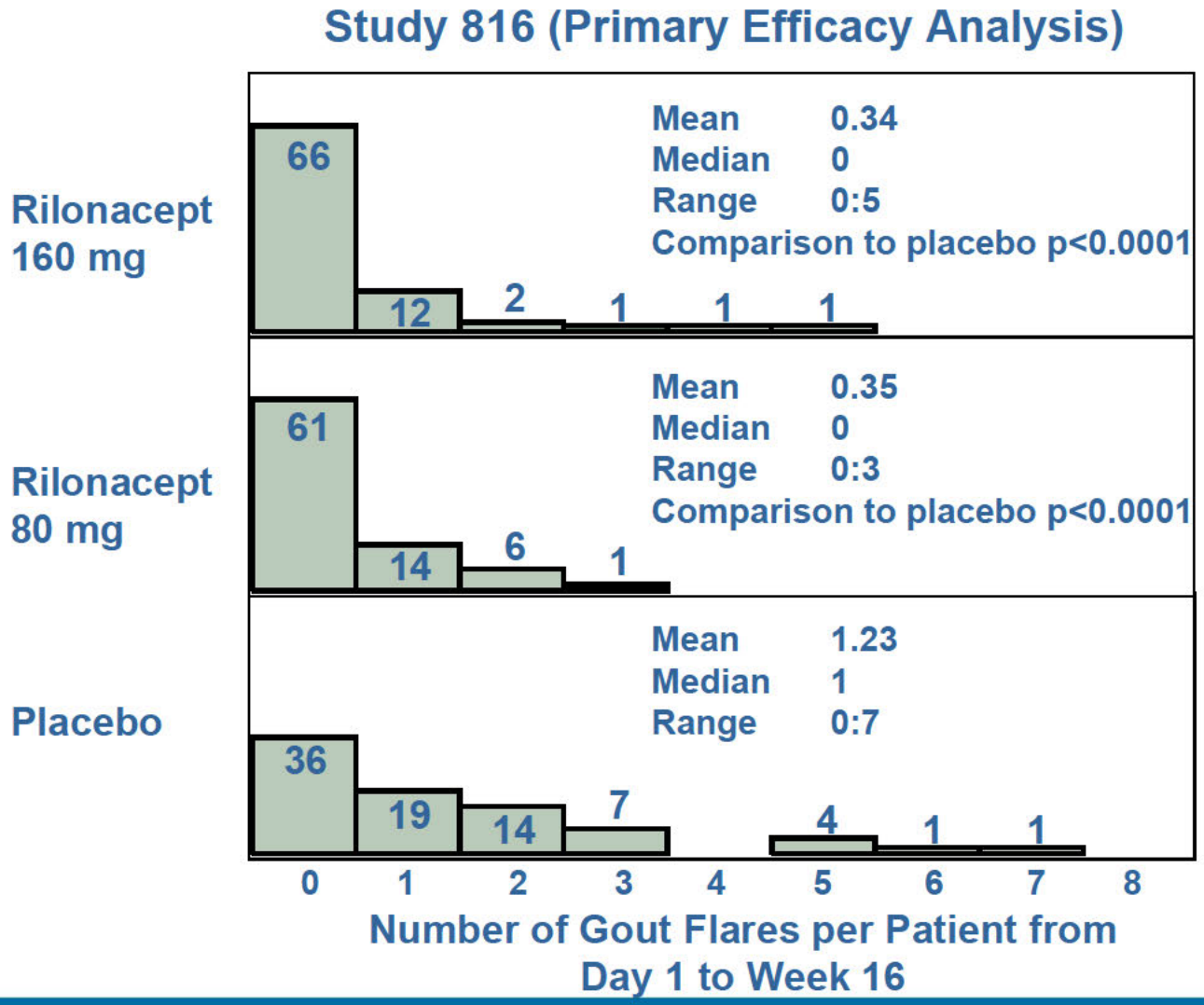


Reduction in mean number of flares

80%

73%

Number of Gout Flares per Patient from Day 1 to Week 16



Reduction in mean number of flares

72%

71.5%

Number Needed to Treat to Benefit / Harm

- Number Needed to Treat (NNT) is the estimated number of patients who need to be treated with the new treatment rather than the control for one additional patient to benefit / harm (as defined by the endpoint under consideration).

- Illustration (not related to the efficacy of rilonacept)

  Drug X cures patients 20% more often than placebo

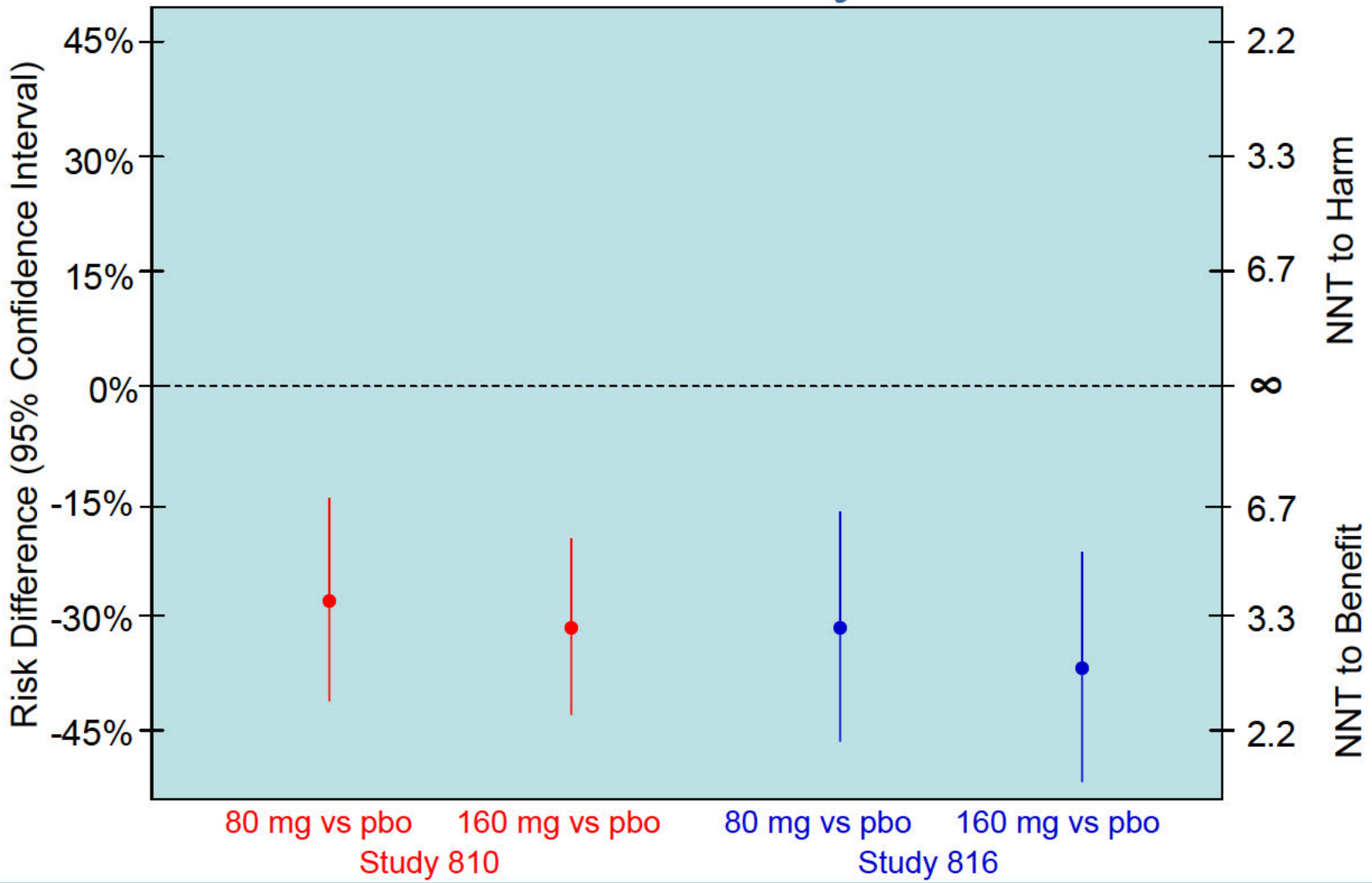
  The NNT to benefit is 1 / 0.20 = 5.

  For every five patients treated with drug X, on average one additional cure is expected.

At least One Flare from Day 1 to Week 16

	Study 810			Study 816		
	Placebo N=79	Rilonacept 80 mg N=80	Rilonacept 160 mg N=81	Placebo N=82	Rilonacept 80 mg N=82	Rilonacept 160 mg N=84
Number of Subjects (%)	37 (47%)	15 (19%)	13 (16%)	46 (56%)	21 (26%)	17 (20%)
Risk Diff (95% CI)		-28% (-42%, -14%)	-31% (-44%, -17%)		-30% (-45%, -16%)	-36% (-50%, -22%)
Number Needed to Treat to Benefit (95% CI)		4 (3, 8)	4 (3, 6)		4 (3, 7)	3 (2, 5)

Proportion of Subjects with At Least One Flare from Day 1 to Week 16

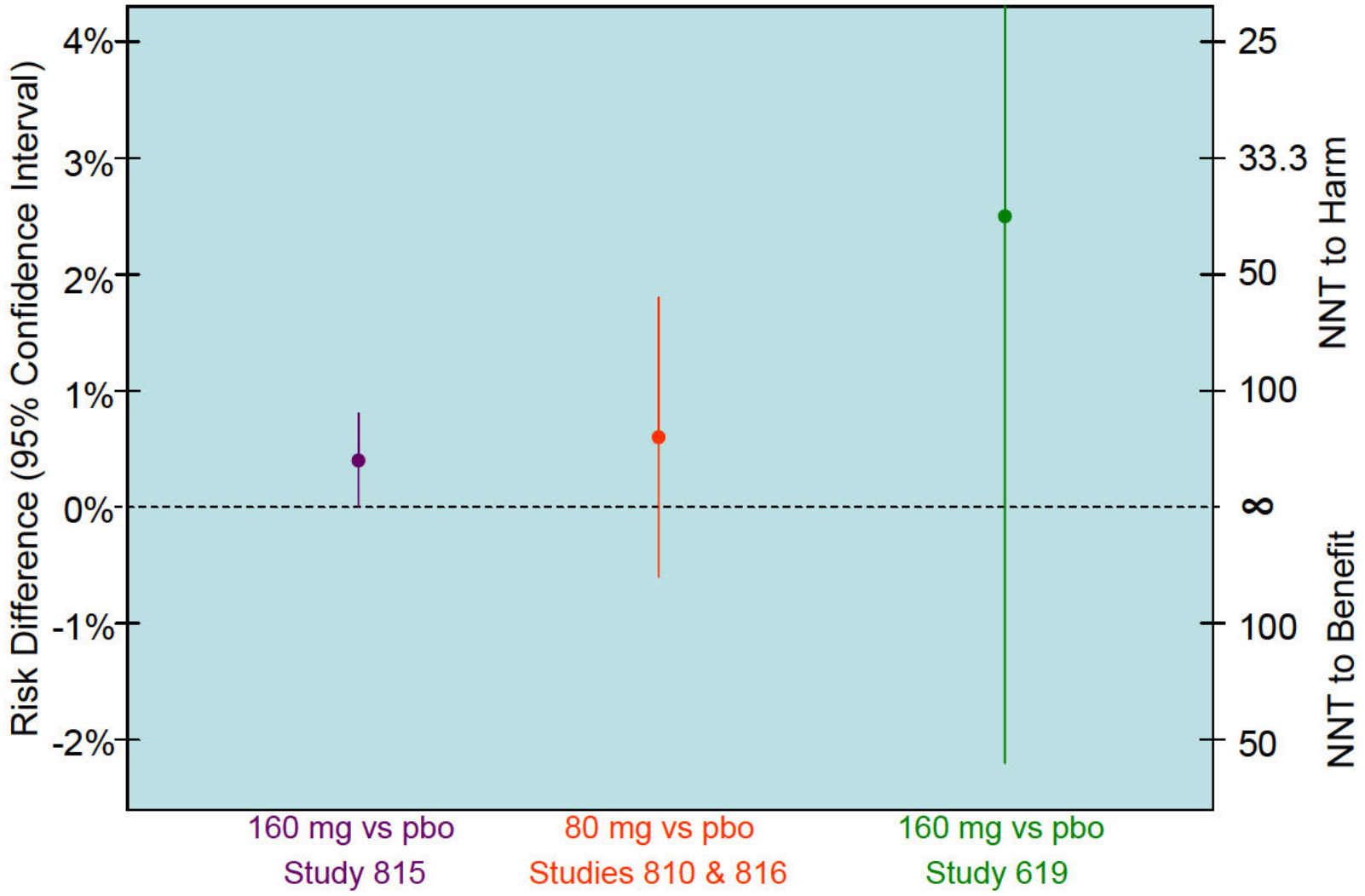


Key: pbo = placebo

Rate of Malignant Neoplasms

	Study 815 (Safety Study)		Studies 810 & 816 Pooled (Phase 3 Efficacy/Safety)			Study 619 (Phase 2 Study)	
	Placebo N=330	Rilonacept 160 mg N=985	Placebo N=161	Rilonacept 80 mg N=162	Rilonacept 160 mg N=165	Placebo N=42	Rilonacept 160 mg N=41
Number of Events (%)	0 (0%)	4 (0.4%)	0 (0%)	1 (0.6%)	0 (0%)	0 (0%)	1 (2.4%)
Risk Diff (95% CI)		.4% (.01%, .8%)		.6% (-.6%, 1.8%)	0 cannot calculate		2.4% (-2.3%, 7.2%)
Number Needed to Treat to Harm (95% CI)		244 (125, 10K)		162 (55, ∞)	cannot calculate		41 (14, ∞)
Number Needed to Treat to Benefit (95% CI)		NA		(170, ∞)	cannot calculate		(44, ∞)

Rate of Malignant Neoplasms



Benefit-Risk

	Study 815	Studies 810 & 816		Study 619
	160 mg vs pbo	80 mg vs pbo	160 mg vs pbo	160 mg vs pbo
At least 1 Flare from Day 1 to Week 16 **NNT to Benefit** **NNT to Harm**	5 (4, 6) NA	4 (3, 6) NA	3 (3, 5) NA	4 (3, 9) NA
Malignancy **NNT to Benefit** **NNT to Harm**	NA 244 (125, 10000)	(170, ∞) 162 (55, ∞)	cannot calculate	(44, ∞) 41 (14, ∞)
Benefit Risk	For every additional 49 patients achieving efficacy, one additional malignancy is expected.	For every additional 41 patients achieving efficacy, one additional malignancy is expected.	cannot calculate	For every additional 10 patients achieving efficacy, one additional malignancy is expected.

Summary

- Efficacy (Studies 810 and 816)
  - Statistically significant reduction in the number of gout flares per patient from day 1 to week 16 with each dose of rilonacept over placebo
    - Mean reduction approximately 0.7 to 0.9 flares
    - No difference between rilonacept doses
  - Caution against use of ratios in describing efficacy (since the mean number of gout flares from day 1 to week 16 was approximately one in the placebo groups)
- Safety (Studies 810, 816, 815 and 619)
  - Suggestion that the risk of malignancy may be increased with rilonacept (point estimates for the NNT to harm ranged from 41 to 244 depending on the study(ies) considered)
- Benefit-Risk
  - Depending on the study(ies) considered, one additional malignancy is expected for every 10 to 49 subjects who do not experience at least one flare from day 1 to week 16

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Efficacy, Safety, and Risk-Benefit Considerations

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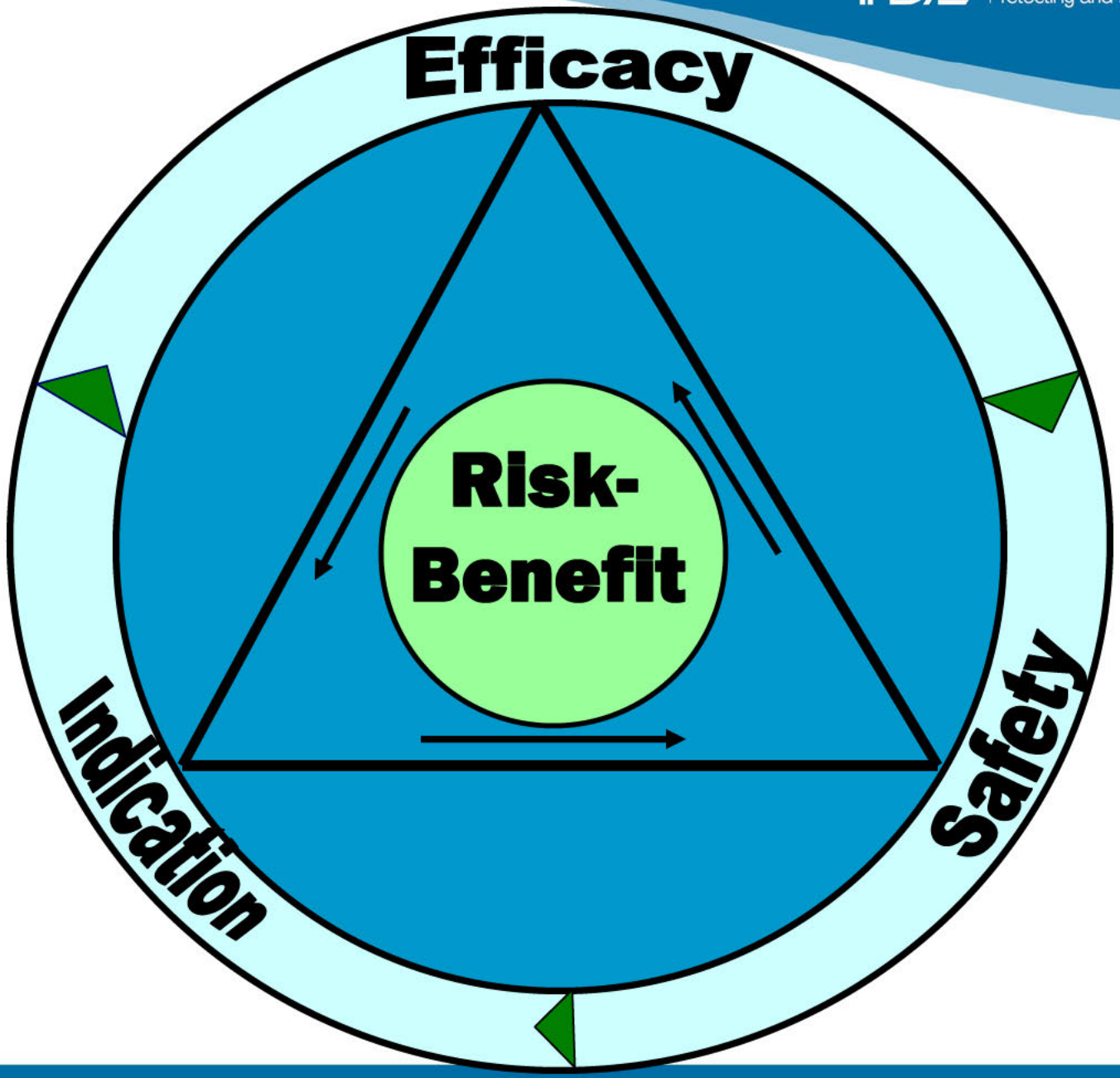
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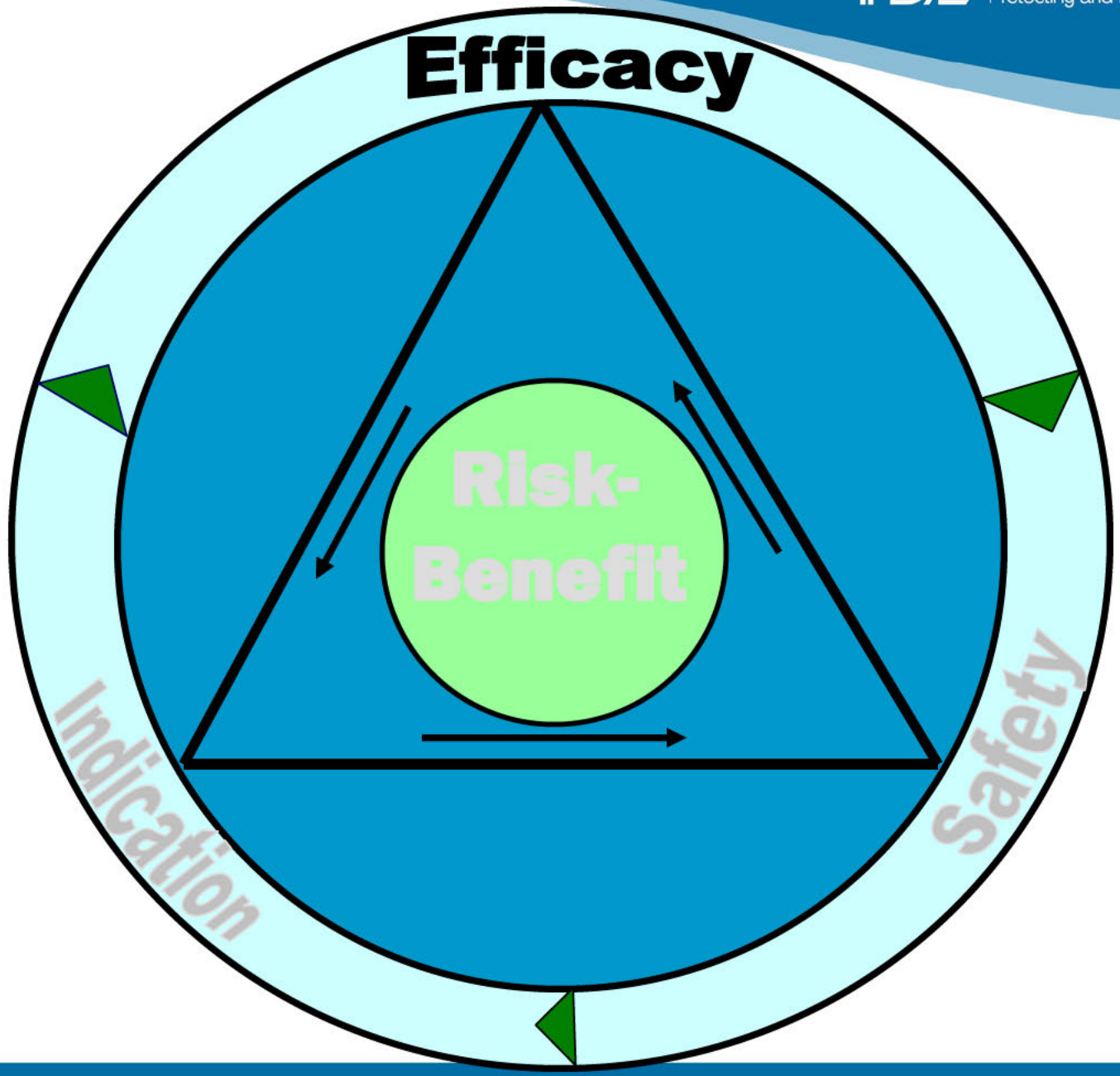
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Phase 3 Studies

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* All patients were initiated on urate-lowering therapy with allopurinol 300 mg titrated upward by 100 mg every 2 weeks until serum uric acid < 6 mg/dL was achieved.

Key: R=randomized; DB=double-blind; PC=placebo-controlled; SC=subcutaneous; QW=once weekly

Efficacy Considerations

- Secondary endpoints
  - Number of gout flare days
- Exploratory endpoints
  - Rescue medication use (NSAIDs & glucocorticoids)

Number of Gout Flare Days Per Patient

Treatment	N	Number of flare days Mean (SD)		Difference from placebo	
		All Flares	Excluding flares >30d	All flares	Excluding flares >30d
Study 810					
RIL 80	80	2.4 (11.4)	1.3 (4.3)	-3.2*	-3.7*
RIL 160	80	1.0 (4.0)	1.0 (3.0)	-4.5*	-4.1*
Placebo	79	5.5 (9.7)	5.0 (9.0)		
Study 816					
RIL 80	82	4.3 (17.1)	1.7 (4.0)	-6.9*	-4.1*
RIL 160	83	1.9 (5.8)	1.5 (4.7)	-9.3*	-4.3*
Placebo	82	11.2 (21.0)	5.7 (8.4)		

* P-value < 0.001 for comparison of rilonacept to placebo

Number of Days Patients Used Rescue Medication

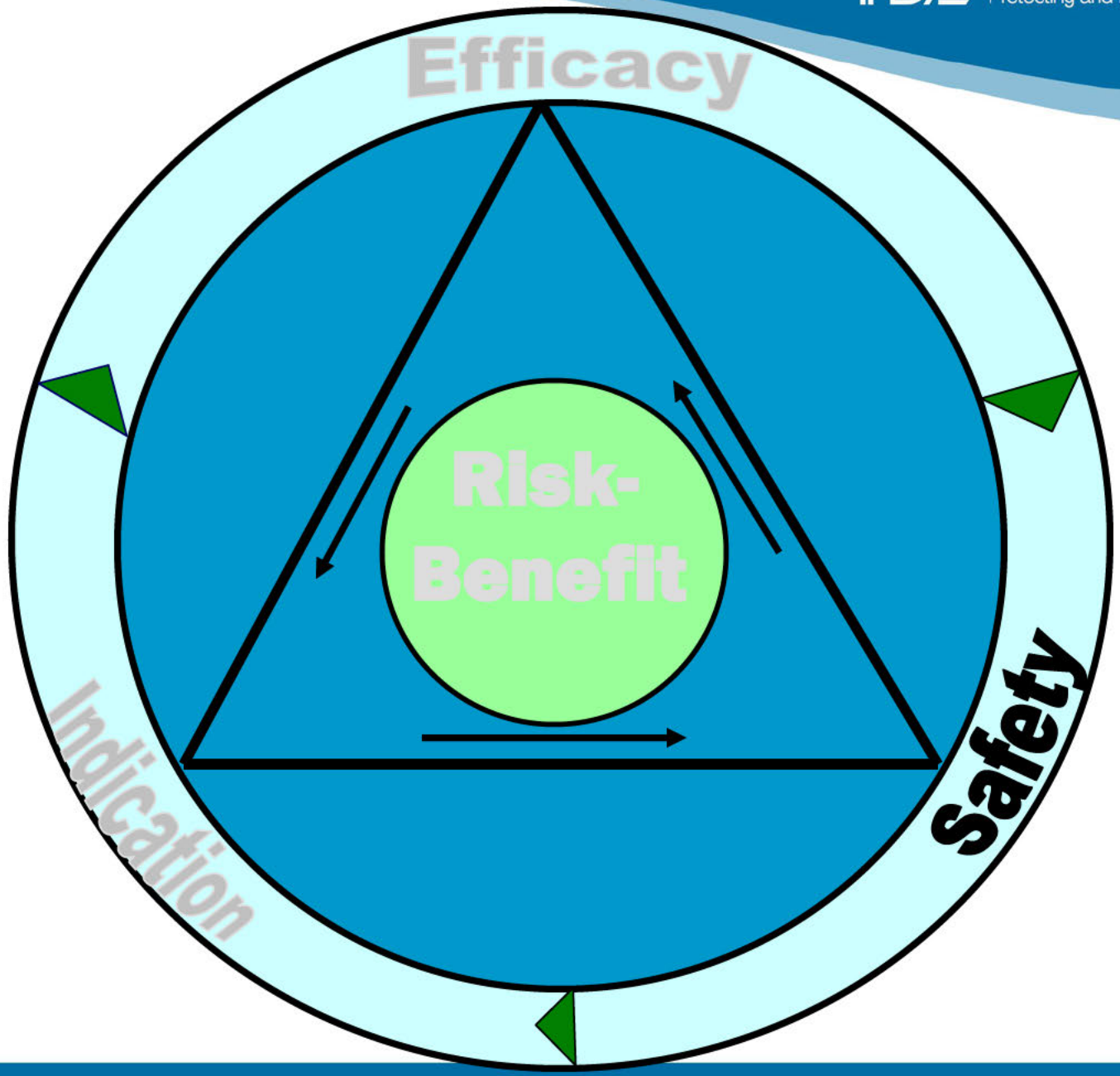
Treatment	N	Number of days Mean (SD)	Difference from placebo
Study 810			
RIL 80	80	2.9 (8.7)	-3.7*
RIL 160	81	1.2 (2.9)	-5.4*
Placebo	79	6.6 (8.8)	
Study 816			
RIL 80	82	2.4 (5.1)	-5.3*
RIL 160	84	1.6 (3.4)	-6.1*
Placebo	82	7.7 (11.8)	

* P-value < 0.0001 for comparison of rilonacept to placebo

Efficacy Considerations

- **Mean number of gout flares per patient**
  - Placebo group experienced a mean of ~ 1 gout flare/patient
  - Rilonacept 80 mg group experienced a mean of ~0.3 flares/patient
  - ~50% of patients in the placebo group did not have a flare
- **Mean number of gout flare days per patient**
  - Rilonacept treatment resulted in ~ 4 less flare days/patient
- **Rescue medication use (NSAIDs & glucocorticoids)**
  - Rilonacept groups used 4 to 5 fewer days of rescue meds

Patients who were prohibited from using NSAIDs and colchicine for flare prophylaxis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Safety Database

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Safety Considerations: Overview

- Deaths
  - 6 deaths reported (placebo: n=3; RIL 160 mg: n=3)
- Serious Adverse Events
  - Overall incidence 3-5% across treatment groups
  - Single occurrences of a wide range of events
- Common Adverse Events
  - Overall incidence 60-66% across treatment groups
  - Injection site reactions most common event
- Adverse Events of Interest
  - Infections
  - Malignancies

Safety Considerations: Infections

System organ class MedDRA preferred term	Rilonacept 80 mg N=162	Rilonacept 160 mg N=1191	Placebo N=533
	n (%)		
All Infections and Infestations	38 (23.5)	241 (20.2)	111 (20.8)
Serious Infections	3 (1.9)	5 (0.4)	3 (0.6)
Appendicitis	1 (<0.1)	0	0
Bacterial arthritis	0	1 (<0.1)	0
Bronchitis	0	1 (< 0.1)	0
Cellulitis	0	1 (<0.1)	2 (0.4)
Diverticulitis	0	1 (<0.1)	0
Liver Abscess	1 (<0.1)	0	0
Pyelonephritis	1 (<0.1)	0	0
Sepsis	0	1 (<0.1)	0
Urinary tract infection	0	1 (<0.1)	0
Viral Meningitis	0	0	1 (0.2)

Safety Considerations: Malignancy

Study *site*	Age/ Sex	Time to diagnosis (days)	# of Doses Received	On-Treatment	Malignancy Type (Preferred Term)
Rilonacept 80 mg [N=162]					
816 *S. Africa*	70/M	32	4	Yes	Gastric Cancer
Rilonacept 160 mg [N=1191]					
815 *US*	71/M	22	3	Yes	Prostate Cancer
815 *US*	56/M	60	9	Yes	Prostate Cancer
815 *US*	72/F	70	10	Yes	Breast Cancer
815 *S. Africa*	52/M	113	15	Yes	Oropharyngeal Cancer
619 *US*	68/M	113	15	Yes	Prostate Cancer

Placebo group (N=533) had no malignancy SAEs reported

Malignancy

Types of cancers not unexpected in a typical gout population

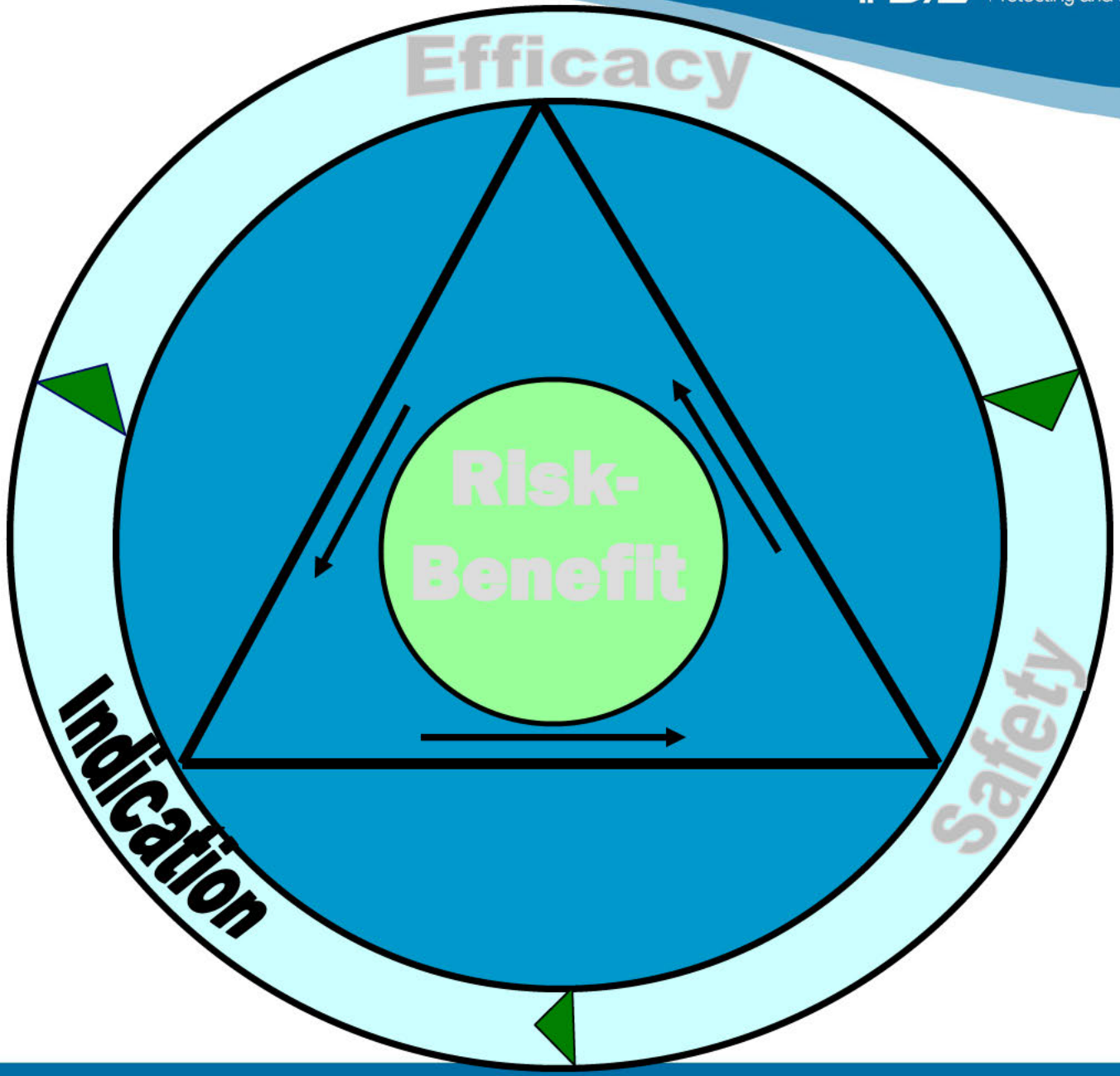
Low number of events over a short duration of treatment

Statistical uncertainty in the risk of malignancy in studies 810, 816, and 619

Most cancers in 160 mg group

Malignancy

Types of cancers not unexpected in a typical gout population	No cancers observed in placebo
Low number of events over a short duration of treatment	Plausible mechanism (immunosuppression)
Statistical uncertainty in the risk of malignancy in studies 810, 816, and 619	Statistically significant increased risk in study 815
	Statistical uncertainty in the risk of malignancy in studies 810, 816, and 619
Most cancers in 160 mg group	160 mg data applicable to 80 mg dose


Efficacy
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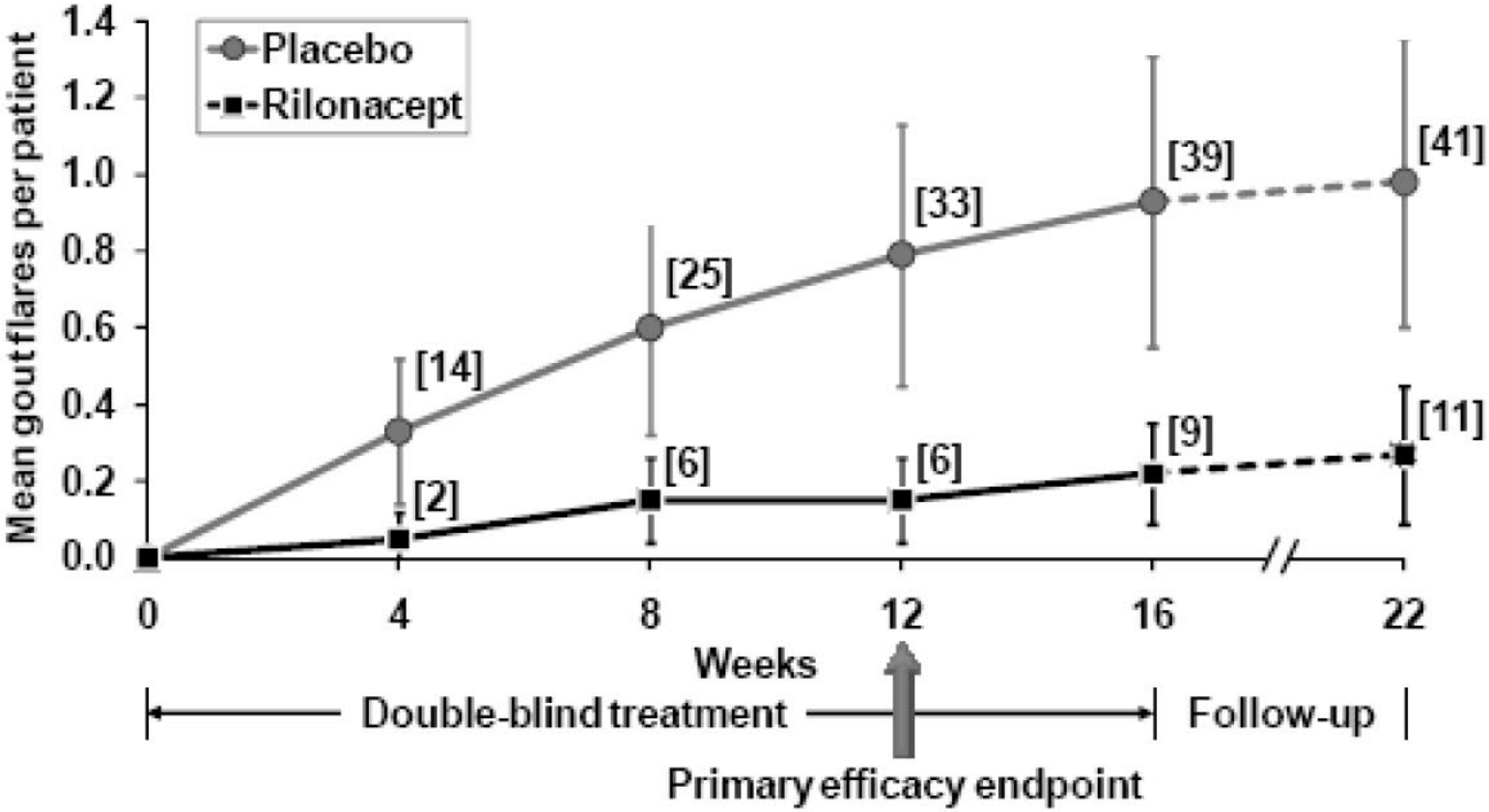
Safety
Indication

Proposed Indication

- Prevention of gout flares *during initiation of uric acid-lowering therapy in* adult patients with gout.
- Rilonacept has *not been studied for longer than 16 weeks* in this clinical setting.
- Because rilonacept has not been studied for more than 16 weeks in patients with gout, *the recommended duration of use is 16 weeks* in patients initiating uric acid-lowering therapy.

Number of Gout Flares per Patient (Study 619)



Percentage of Patients With At Least One Flare by Time Period After Initiation of Allopurinol Treatment – Study 810

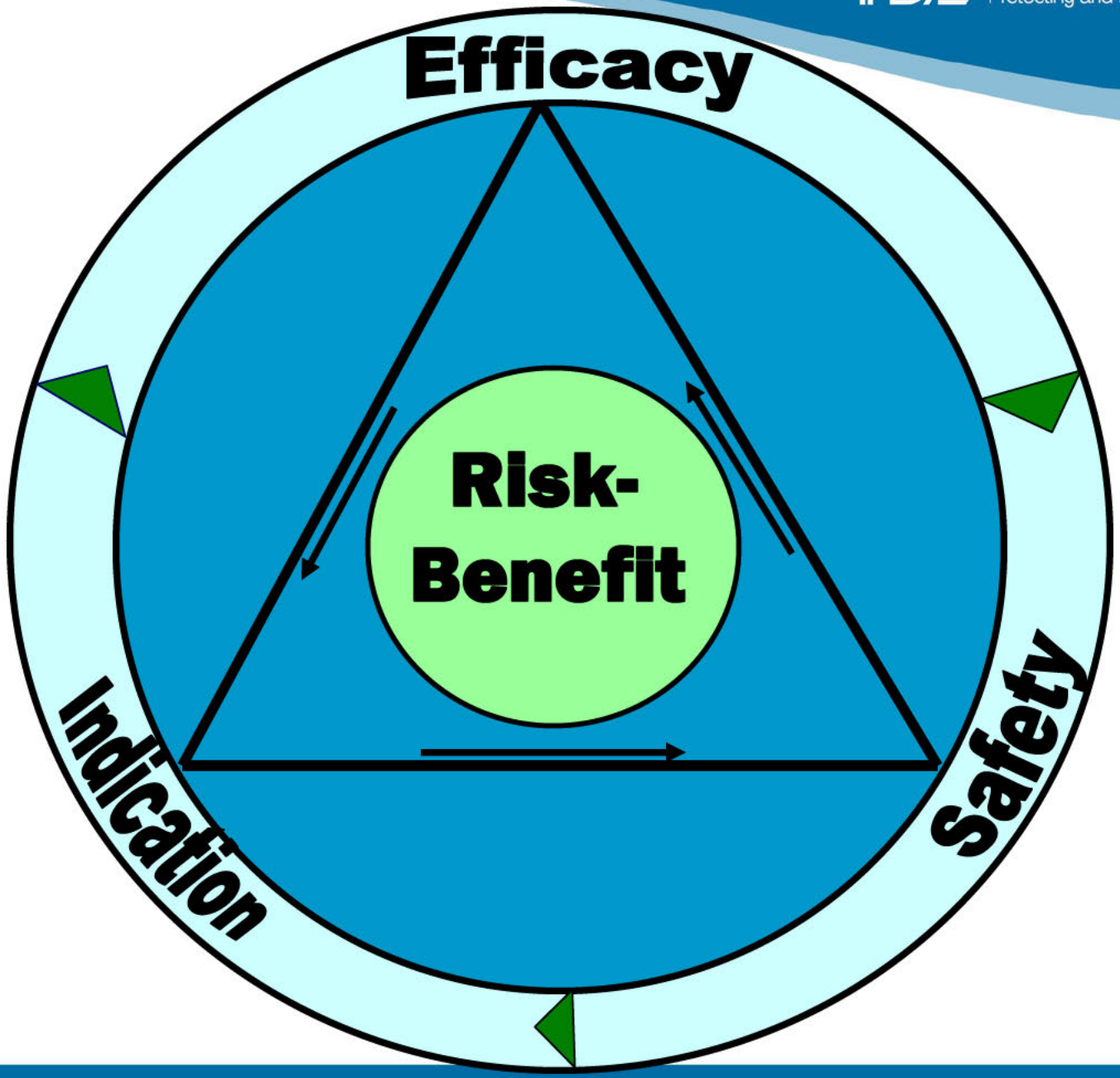
	Placebo		Rilonacept 80 mg		Rilonacept 160 mg	
	N	%	N	%	N	%
Day 1 to Week 4	79	25.3	80	6.3	80	6.3
Week 4 to Week 8	68	29.4	78	10.3	76	6.6
Week 8 to Week 12	61	19.7	69	8.7	72	2.8
Week 12 to Week 16	60	16.7	65	1.5	70	5.7
Week 16 to Week 20	54	22.2	61	13.1	66	16.7

Percentage of patients with flares is based on the number of patients in a treatment group at the beginning of the specified time period.

Percentage of Patients With At Least One Flare by Time Period After Initiation of Allopurinol Treatment – Study 816

	Placebo		Rilonacept 80 mg		Rilonacept 160 mg	
	N	%	N	%	N	%
Day 1 to Week 4	82	43.9	82	19.5	83	14.5
Week 4 to Week 8	76	25.0	79	6.3	79	8.9
Week 8 to Week 12	71	16.9	77	2.6	77	6.5
Week 12 to Week 16	70	17.1	76	2.6	76	2.6
Week 16 to Week 20	67	9.0	71	21.1	71	18.3

Percentage of patients with flares is based on the number of patients in a treatment group at the beginning of the specified time period.


Efficacy
Risk-
Benefit
Indication
Safety

Gout Management

Intercritical Gout

- Urate-lowering therapy
  - Start low, go slow
  - Start high and use prophylaxis
- Prophylaxis against acute gout flares
  - Usual therapies: NSAIDs and colchicine
  - Duration: Until no acute attacks for 3-6 months
    - Risk of flares ↓ with continuing urate-lowering therapy

Acute Gout Flares

- Painful, but self-limited, treatable with NSAIDs, colchicine, corticosteroids in most patients

Risk-Benefit Considerations

Efficacy

- 2 studies with statistically significant reductions in mean number of gout flares per patient (primary endpoint) and in various secondary/exploratory endpoints

- Clinical significance of treatment effect size unclear
- Studied patient population not one that is refractory to or intolerant of usual gout flare prophylaxis
- Gout flares are typically self-limited, respond to usual anti-inflammatory therapies, and occur with decreasing incidence as urate-lowering therapy continues
- 16 week treatment duration may not be the optimal vulnerable period for increased risk of flares

Risk-Benefit Considerations

Safety	
• Restricted duration to minimize unnecessary exposure to biologic immunosuppressant	• Possible increased risk in malignancies with rilonacept
• No substantial increase in serious infections over 16 weeks	• No long-term safety data beyond 16 weeks in gout population

Concluding Remarks

- Appearance of several novel drugs in the therapeutic pipeline
  - Existing therapies not optimally utilized
  - Addition of new therapies alone will not solve this problem
- IL-1 inhibition may have a role in gout
  - Patients who cannot tolerate or do not respond to traditional agents

FDA Arthritis Advisory Committee Meeting May 8, 2012 – Charge to Committee

sBLA 125249: Arcalyst (rilonacept) for Prevention of Gout Flares During Initiation of Uric Acid-Lowering Therapy

Sarah Yim, M.D.

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Center for Drug Evaluation and Research

Risk-Benefit Considerations

- Patient population
  - Not a refractory or particularly difficult-to-treat population
  - Half of patients receiving no treatment did not even experience a flare
- Efficacy limitations
  - Apparent treatment effect sizes represent effect of rilonacept vs. no treatment
  - Treatment period of 16 weeks may not be long enough; patients flared after treatment
- Safety limitations
  - Duration of 16 weeks may not be adequate to demonstrate many toxicities

Approval of an Application 21 CFR 314.105 (c)

- "FDA will approve an application after it determines that the drug meets the statutory standards for safety and effectiveness, manufacturing and controls, and labeling."

Efficacy Standard 21 CFR 314.125 Refusal to Approve an Application

(b)(5) "…substantial evidence consisting of adequate and well-controlled investigations…that the drug product will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling."

Safety Standard
21 CFR 314.125 Refusal to Approve an Application

(b)(2) "…do not include adequate tests by all methods reasonably applicable to show whether or not the drug is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling."

(b)(3) "The results of the test show that the drug is unsafe for use under the conditions prescribed, recommended, or suggested in its proposed labeling or the results do not show that the drug product is safe for use under those conditions."

(b)(4) "There is insufficient information about the drug to determine whether the product is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling."

Discussion Item #1: Efficacy of Rilonacept

- Discuss the efficacy data of rilonacept for the prevention of gout flares
  - Include a discussion of the effect of rilonacept on flare frequency and duration, and whether the observed treatment effect provides adequate justification for the use of rilonacept to prevent gout flares in a gout population that is not intolerant of or refractory to NSAIDs and/or colchicine
  - Include a discussion of the clinical applicability of the proposed indication, addressing whether the efficacy data support a treatment duration of 16 weeks

Discussion Item #2: Safety of Rilonacept

- Discuss the safety profile of rilonacept for the prevention of gout flares
  - Include a discussion of the malignancy imbalance
  - Include a discussion of the adequacy of the currently available 16-week safety database to support the proposed use

Item #3: Efficacy Voting Question

- Are the available efficacy data adequate and supportive of approval of rilonacept for the prevention of gout flares during the initiation of uric acid-lowering therapy in adult patients with gout?

Item #4: Safety Voting Question

- Are the available safety data adequate and supportive of approval of rilonacept for the prevention of gout flares during initiation of uric acid-lowering therapy in adult patients with gout?

Item #5: Approvability Voting Question

- Do the efficacy and safety data support the approval of rilonacept 80 mg subcutaneously once weekly (following a 160 mg loading dose) for 16 weeks for the prevention of gout flares during the initiation of uric acid-lowering therapy in adult patients with gout?